Applied Chemistry of Western and Chinese Medicines

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Who am I

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- PhD in Chemistry (CityU) 2003

Kinetics and mechanisms of redox reactions of ruthenium-oxo complexes

- BSc (1st Hons) in Applied Chemistry (CityU) 1998

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1. Basic chemical and biochemical concepts in pharmaceutical chemistry
2. Chemistry and mechanisms of different kinds of drugs
3. Drug manufacturing process
4. Basic requirements of Good Manufacturing Practice and quality control in Western medicines

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Basic Chemical and Biochemical Concepts in Pharmaceutical Chemistry

What is Medicinal Chemistry ?

- Medicinal Chemistry is a chemistry-based discipline, involving aspects of biological, medical and pharmaceutical sciences.
- It is concerned with
  - the invention, discovery, design, identification and preparation of biologically active compounds,

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- the study of their metabolism, the interpretation of their mode of action at the molecular level ,
- the construction of structure-activity relationships (SARs).

- Medicinal chemistry also involves the discovery of new chemical entities for the treatment of diseases.
- Also the systematic study of the structure-activity relationships of the active compounds.

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Origins of Medicinal Chemistry

Year	Types of drug discovered
Early	Natural products
1875	Salicylic acid (a possible cure for typhoid fever)
1898	Diacetylmorphine (as a pain reliever)
1899	Aspirin (as an antipyretic without the unpleasant side effects)

- Medicinal chemistry began.
- Fast development was observed from 1900's to 1960's.

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Year	Types of drug discovered
1920's – 1930's	Anesthetics, Hypnotics, Analgesics were used extensively
1930's	Penicillin (the first antibiotics)
1940's	Nitrogen mustard (the first drug used for treating cancer)
1960's	Oral steroidal contraceptive agents
1979	Nifedipine (calcium Channel Blocker)
1981	Captopril (angiotensin Converting Enzyme Inhibitor, ACE)

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What is a drug ?

- As defined by law, the difference between medicines and drugs is that
  - medicines have fairly negligible toxicities,
  - drugs are habit-forming substances that may lead to some serious adverse effects even though it is still initially used to cure diseases.
- Drugs are pharmaceutical agents that design and synthesize by medicinal chemists having
  - a desired biological effect on the human body,
  - some other living system.

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- So no drugs are totally safe.
- The dose level determines whether they will act as medicines or poisons.
- Useful drugs show toxicity against foreign or abnormal cells but not against normal host cells.
- Drugs may be mere chemicals, but they are entering a world of chemical reactions with which they interact.
- This is more a result of where they act in the body.
  - The drug targets.

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The importance of drug in human society

- Drugs have irrevocably changed the fabric of society by
  - improving the individual quality of life
  - improving the individual life expectancy
- Examples
  - Bacterial and virus infections
    - ✓ Polio (小兒麻痺症), smallpox (天花), tuberculosis (結核病) and related diseases have, to a very major extent, become minor public health concerns.

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- An increase in life expectancy
  - ✓ led to a shift in population demographics toward a more healthy, elderly population.
- Drug regimens for birth control
  - ✓ have improved individual life choices and the quality of life.
- HIV protease and reverse transcriptase inhibitors
  - ✓ from fatal to a potentially chronic one.
- Cancer
  - ✓ viewed as a potentially chronic, rather than fatal disease.

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Classification of drugs

- Drugs used in medicine generally divided into classes or groups on the basis as their
  - origin
  - uses
  - chemical structures
  - mechanisms
  - target systems
  - target molecules

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On the basis of origin

- Natural, synthetic and semi-synthetic compounds.
- Natural compounds
  - Materials obtained from both plant and animal
  - e.g. vitamins, hormones, amino acids, antibiotics, alkaloids, glycosides, etc
- Synthetic compounds
  - Either pure synthesis or synthesis naturally occurring compounds
  - e.g. morphine, atropine, steroids and cocaine

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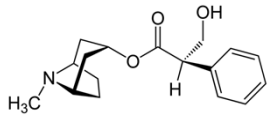
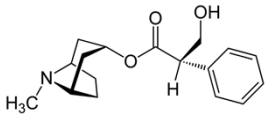
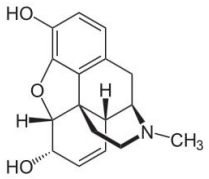


D-isomer

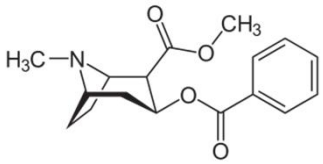


L-isomer

atropine



morphine



cocaine

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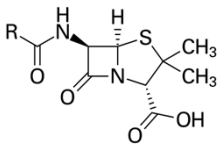
- Semi-synthetic compounds
  - Some compounds either can not be purely synthesized or can not be isolated from natural sources in low cost.
  - the natural intermediate of such drugs could be used for the synthesis
  - e.g. semi-synthetic penicillin



penicillin

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On the basis of uses

- According to the medical uses
  - Pharmacodynamic agents
    - ✓ Drugs that act on the various physiological functions of the body.
    - ✓ e.g. general anaesthetic, hypnotic and sedatives, analgesic, etc.
  - Chemotherapeutic agents
    - ✓ Those drugs which are used to fight pathogenic.
    - ✓ e.g. sulphonamides, antibiotics, antimalarial agents, antiviral, anticancer, etc.

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- **According to the treatment of diseases**
  - **Infectious diseases**
    - ✓ Transmitted from person to person by outside agents.
    - ✓ e.g. bacteria, viruses, fungi, parasites.
  - **Non-infectious diseases**
    - ✓ Disorders of the human body caused by genetic malfunction, environmental factors, stress, old age etc.
    - ✓ e.g. diabetes, heart disease, cancer, haemophilia, asthma, mental illness, stomach ulcers, arthritis.

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- **Non-diseases**
  - ✓ e.g. alleviation of pain (analgesic), prevention of pregnancy (contraception) , anesthesia.

On the basis of chemical structures

- **Drugs which have same drug action and pharmacological effect have a basic skeletal structure and a minute variation in the branching.**
- **This is why some drugs have more potential than the other.**

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On the basis of mechanisms (action)

- **Each drug has its own way of generating response called drug action.**
- **Drug action is more specified according to how it generates a response.**
- **For example, there are lots of medicines to treat hypertension but each type of drug has different drug action.**
- **All the hypertension medicines reduce the blood pressure but in a different pathway.**

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On the basis of target system

- **Drugs can be classified according to whether they affect a certain target system in the body.**
  - **e.g. protein target**

On the basis of target molecule

- **Some drugs are classified according to the molecular target with which they interact.**
  - **e.g. one type of enzyme**

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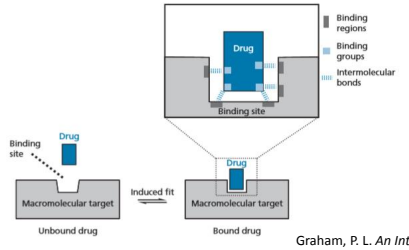
Intermolecular forces of drug

Intermolecular binding forces

- The interaction of a drug with a macromolecular target involves a process known as binding.
- There is usually a specific area where this takes place, known as the binding site.



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- Some drugs react with the binding site and become permanently attached via a covalent bond.
- However, most drugs interact through weaker forms of interaction known as intermolecular bonds.
  - Ionic or electrostatic bonds
  - Hydrogen bonds
  - Van der Waals interactions
  - Dipole-dipole interactions
  - Hydrophobic interactions

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- Those bonds or interactions are weak.
- They can be broken easily and form again.
- An equilibrium takes place between the drug being bound and unbound to its target.
- The binding forces are strong enough to hold the drug for a certain period of time to let it have an effect on the target.
- However they are weak enough to allow the drug to depart once it has done its job.

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- The length of the time drug remains at its target depend on the number of intermolecular bonds involved in holding it there.
- So the relative strength of binding forces is also an important factor.
- Functional groups present in the drug can be important in forming intermolecular bonds with the target binding site.
  - They are called the binding groups
- The carbon skeleton of the drug also plays an important role in binding the drug to its target through van der Waals interactions.

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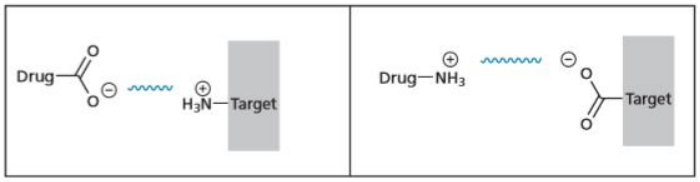

Ionic bond

Hydrogen bond

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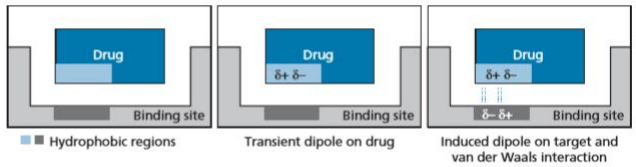
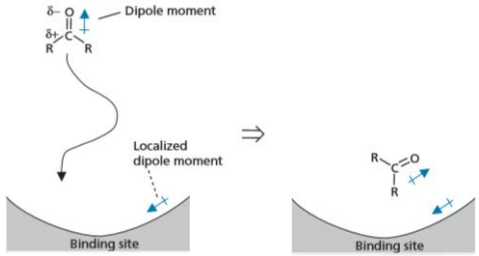


Van der Waals interaction



Dipole-dipole interaction

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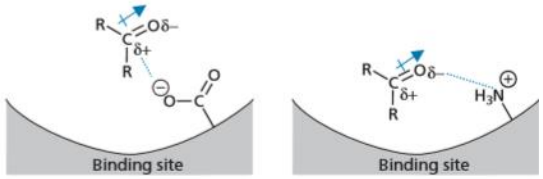
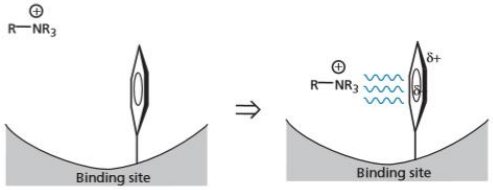


Ion dipole interaction



Induced dipole interaction

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Repulsive interaction

- **Repulsive interactions are also important.**
- **Otherwise, there would be nothing to stop molecules trying to merge with each other.**
- **If molecules come too close, their molecular orbitals start to overlap and this results in repulsion.**
- **Other forms of repulsion are related to the types of groups present in both molecules.**

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Role of water

- A crucial feature that is often overlooked when considering the interaction of a drug with its target is the role of water.
- The macromolecular targets in the body exist in an aqueous environment,
  - the drug has to travel through that environment in order to reach its target.
  - both the drug and the macromolecule are solvated with water molecules before they meet each other.

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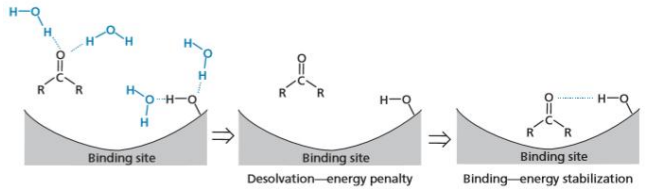
- The water molecules have to be stripped away before the interactions described above can take place.



- This requires energy.
  - If the energy required to desolvate both the drug and the binding site is greater than the stabilization energy gained by the binding interactions, then the drug may be ineffective.

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Structures and functions of drug targets

- An understanding of how a macromolecule operates is crucial.
  - If one is going to design an effective drug that will interfere with that process.
  - For example, understanding the mechanism of how enzymes catalyse reactions.
- For example, understanding the mechanism of how enzymes catalyse reactions
  - extremely important in the design of many important drugs.

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Cell structure

- Life is made up of cells,
  - so drugs must act on cells.
- All cell in human body contain a boundary wall called cell membrane
  - which encloses the contents of the cell — the cytoplasm.
- The cell membrane consists of two identifiable layers.
  - Each of which is made up of an ordered row of phosphoglyceride molecules, such as phosphatidylcholine (lecithin).

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- The outer layer of the membrane is made up of phosphatidylcholine.
- The inner layer is made up of phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol.

- Each phosphoglyceride molecule consists of a small polar head-group and two long, hydrophobic (waterhating) chains.

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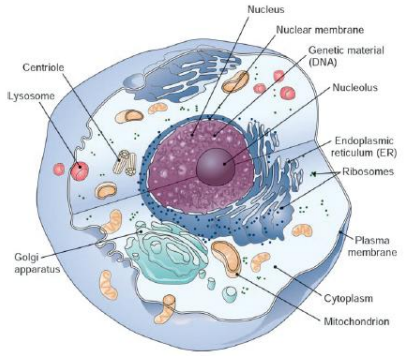

a typical mammalian cell

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- The two layers of phospholipids are arranged such that
  - the hydrophobic tails point towards each other and form a fatty, hydrophobic centre
  - the ionic head-groups are placed at the inner and outer surfaces of the cell membrane
- This is a stable structure
  - because the ionic, hydrophilic head-groups interact with the aqueous media inside and outside the cell
  - the hydrophobic tails maximize hydrophobic interactions with each other and are kept away from the aqueous environments.

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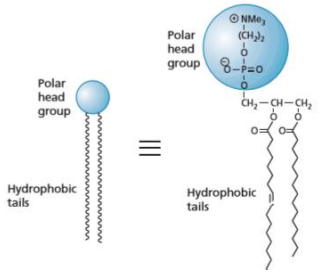
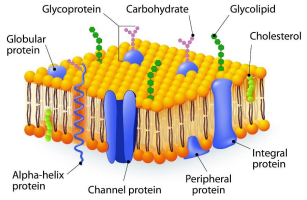
- The overall result of this structure is
  - to construct a fatty barrier between the cell's interior and its surroundings.



phosphoglyceride structure



cell membrane

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Protein: structure and function

- The majority of drugs used in medicine are targeted to proteins.
  - enzymes
  - receptors
  - transport proteins
- It is important to understand protein structure in order to understand drug action on proteins.
- Proteins have four levels of structure.
  - They are primary, secondary, tertiary and quaternary

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Primary structure

- The primary structure is the order in which the individual amino acids making up the protein are linked together through peptide bonds.

- The peptide bond in proteins is planar in nature as a result of the resonance structure.
  - This gives the peptide bond a significant double bond character which prevents rotation.

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- As a result, bond rotation in the protein backbone is only possible for the bonds on either side of each peptide bond.

Synthesized in the human body			Essential to the diet		
Amino acid	Codes Three-letter	One-letter	Amino acid	Codes Three-letter	One-letter
Alanine	Ala	A	Histidine	His	H
Arginine	Arg	R	Isoleucine	Ile	I
Asparagine	Asn	N	Leucine	Leu	L
Aspartic acid	Asp	D	Lysine	Lys	K
Cysteine	Cys	C	Methionine	Met	M
Glutamic acid	Glu	E	Phenylalanine	Phe	F
Glutamine	Gln	Q	Threonine	Thr	T
Glycine	Gly	G	Tryptophan	Trp	W
Proline	Pro	P	Valine	Val	V
Serine	Ser	S			
Tyrosine	Tyr	Y			

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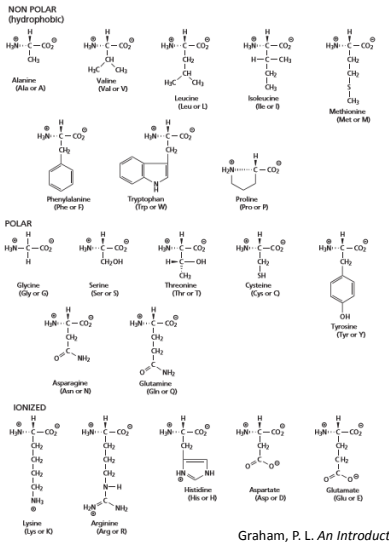

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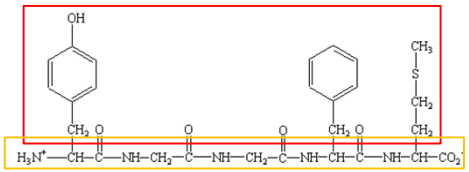
side chain

backbone



primary structure of Met-enkephalin

Secondary structure

- The secondary structure of proteins consists of regions of ordered structure adopted by the protein chain.
- There are three main secondary structures.
  - α-helix, β-pleated sheet and β-turn.

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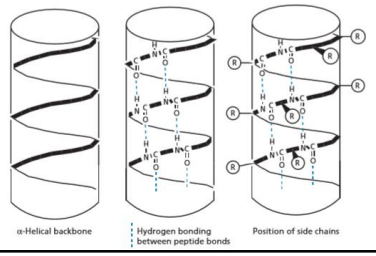
- The α-helix
  - The α-helix results from coiling of the protein chain such that
    - ✓ the peptide bonds making up the backbone are able to form hydrogen bonds between each other.
  - These hydrogen bonds are directed along the axis of the helix.



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- The β-pleated sheet
  - The β-pleated sheet is a layering of protein chains one on top of another.
  - The structure is held together by hydrogen bonds between the peptide chains.
    - ✓ The side chains are situated at right angles to the sheets to reduce steric interaction
    - ✓ The chains in β-sheets can run in opposite directions (antiparallel) or in the same direction (parallel).

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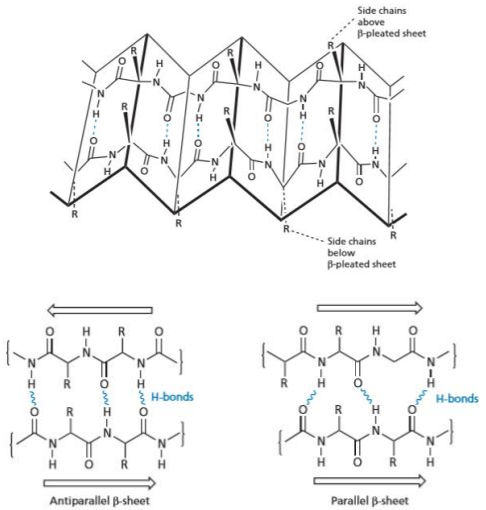

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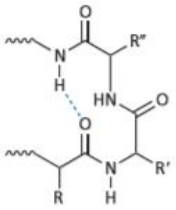
- The β-turn
  - A β-turn allows the polypeptide chain to turn abruptly and go in the opposite direction.
  - This is important in allowing the protein to adopt a more globular compact shape.
  - A hydrogen bonding interaction between the first and third peptide bond of the turn is important in stabilizing the turn.



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Tertiary structure

- Tertiary structure is the overall three-dimensional shape of a protein.
- The tertiary structure of enzymes and receptors is crucial to
  - their function and
  - their interaction with drugs.
- Protein contains a range of different chemical functional groups along its length.
- These can interact with each other such that there is either an attractive interaction or a repulsive interaction.

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- The protein will twist and turn
  - to minimize the unfavorable interactions and
  - maximize the favorable ones
  - until the most stable shape or conformation is found.
- The bonding interactions involved in tertiary structure are the same as the intermolecular bonds mentioned before.

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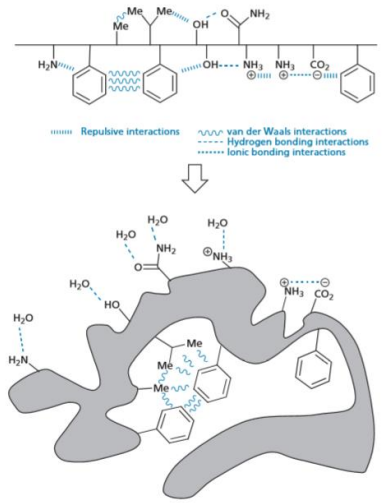

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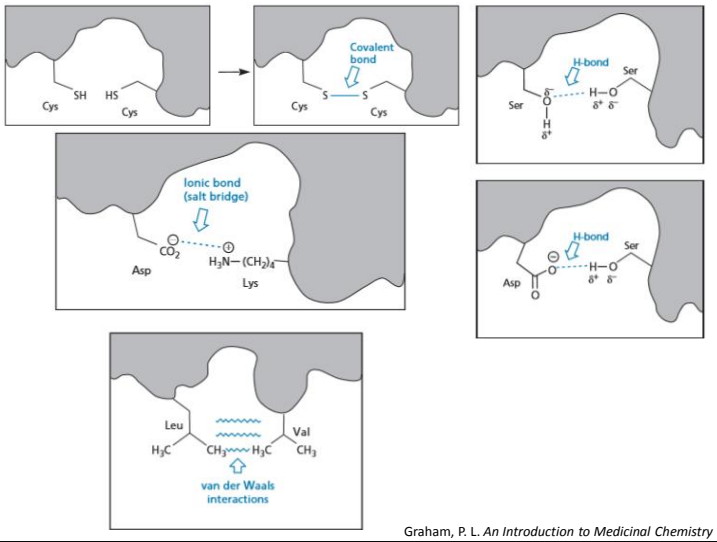

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Quaternary structure

- Only proteins that are made up of a number of protein subunits have quaternary structure.
- Ionic bonding can be important to quaternary structure.
- Hydrophobic and van der Waals interactions also have a role to play.
- There is a distinct advantage for two protein molecules to form a dimer such that
  - the two hydrophobic areas face each other rather than be exposed to an aqueous environment.

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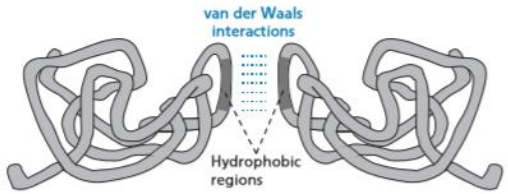

Translation and post-translation modifications

- The process by which a protein is synthesized in the cell is called translation.
- These modifications can have wide range of effects.
  - The N-terminals of many proteins are acetylated, making these proteins more resistant to degradation.

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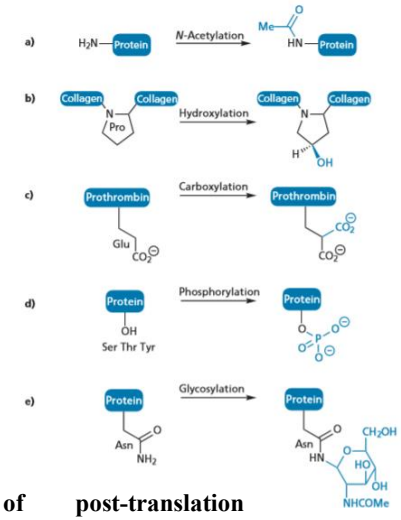

Examples of post-translation modifications carried out on proteins

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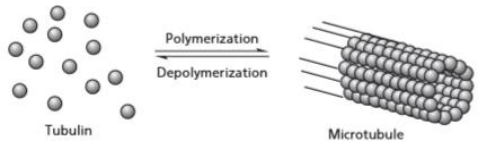
Protein function

- **Structural proteins**
  - Structural proteins do not normally act as drug targets.
  - However, the structural protein tubulin is an exception.
  - Tubulin molecules polymerize to form small tubes called microtubules in the cell's cytoplasm.



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- These microtubules have various roles within the cell.
  - ✓ maintenance of shape
  - ✓ exocytosis
  - ✓ release of neurotransmitters
  - ✓ the mobility of cells
- Tubulin plays an important role in cell division.

- **Transport proteins**
  - Transport proteins are present in the cell membrane and act as the cell's "smugglers".

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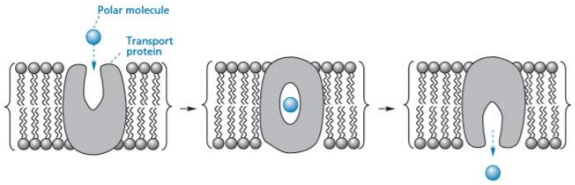
- ✓ Smuggling the important chemical building blocks of amino acids, sugars, and nucleic acid bases across the cell membrane
- ✓ So that the cell can synthesize its proteins, carbohydrates, and nucleic acids.

- They are also important in transporting important neurotransmitters back into the neuron.



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Enzymes: structure and function

- **Enzymes are proteins which act as the body's catalysts.**
  - Speed up a chemical reaction without being consumed themselves.
  - Without them, the cell's chemical reactions would either be too slow or not take place at all.
- **Example**
  - The reduction of pyruvic acid to lactic acid.
  - Takes place when muscles are over-exercised.
  - Catalysed by an enzyme called lactate dehydrogenase.

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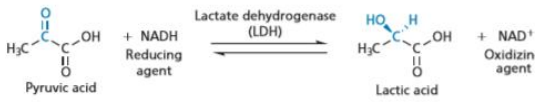
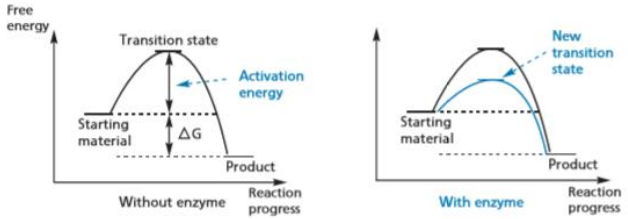


- How enzymes can do it ?



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- How do enzymes catalyse reactions ?
  - Enzymes provide a reaction surface and a suitable environment.
  - Enzymes bring reactants together and position them correctly.
    - ✓ So that they easily attain their transition state configurations.
  - Enzymes weaken bonds in the reactants.
  - Enzymes may participate in the reaction mechanism.
  - Enzymes form stronger interactions with the transition state than with the substrate or the product.

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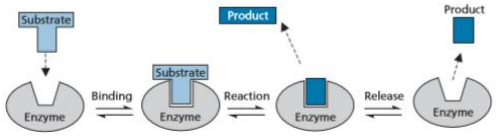
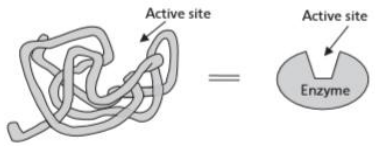
Active site of enzyme

- The active site of an enzyme has to be on or near the surface of the enzyme if a substrate is to reach it.





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- The interactions which bind substrates to the active sites of enzymes include
  - ionic bonds
  - hydrogen bonds
  - dipole-dipole interaction
  - ion-dipole interaction
  - van der Waals interaction
  - hydrophobic interaction

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- In the past,
  - a substrate fitted its active site in a similar way to a key fitting a lock.
  - Fischer's lock and key hypothesis
  - Both the enzyme and the substrate were seen as rigid structures, with the substrate (the key) fitting perfectly into the active site (the lock).
- Recently,
  - the substrate is not quite the ideal shape for the active site.
  - It forces the active site to change shape when it enters.

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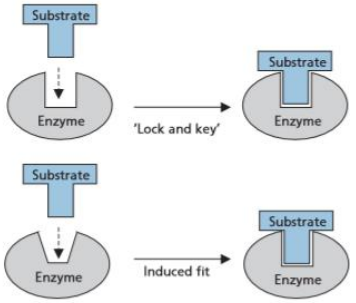
- It likes a kind of moulding process.
- Koshland's theory.
- Substrate induces the active site to take up the ideal shape to accommodate it.



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Receptors: structure and function

- Receptors are proteins which are the most important drug targets in medicine.
- Receptors are to be a communication system between cells.
- Control and communication come primarily from the brain and spinal column (the central nervous system),
  - which receive and send messages via a vast network of nerves.
- The message as being an electrical pulse which travels down the nerve cell (neuron) towards the target.

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- Neurons do not connect directly to their target cells.
- They stop just short of the cell surface.
- The distance is minute, about 100 Å,
  - but it is a space that the electrical "pulse" is unable to jump.
- There has to be a method of carrying the message across the gap between the nerve ending and the target cell.
- The problem is solved by the release of a chemical messenger called a neurotransmitter from the nerve cell.

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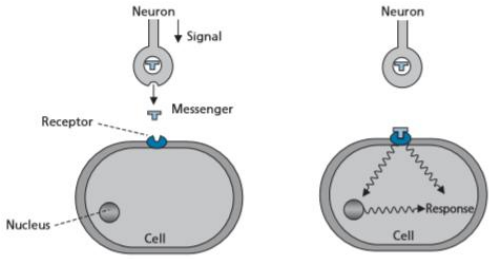
- It binds and interacts with a specific protein (receptor) in the membrane.
- So drugs can affect this communication.



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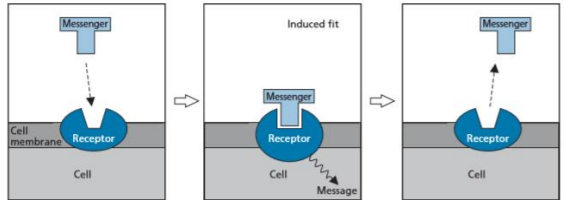
- When the chemical messenger fits into this site it "switches on" the receptor molecule and a message is received.
- When the messenger fits the binding site of the protein receptor it causes the binding site to change shape.
- This is known as the "induced fit".



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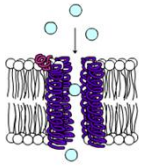
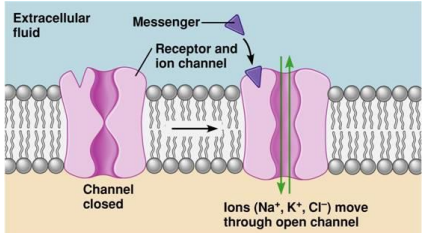
Ion channel receptors

- Some neurotransmitters operate by controlling ion channels.
- Ion channels are complexes made up of five protein subunits which traverse the cell membrane.
- The centre of the complex is hollow and lined with polar amino acids to give a hydrophilic tunnel, or pore.



67

- Ions can cross the fatty barrier of the cell membrane by moving through these hydrophilic channels or tunnels.
- There has to be a "lock gate" that can be opened or closed as required.



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G-protein coupled receptors

- The G-protein-coupled receptors are some of the most important drug targets in medicinal chemistry.
- Around 30% of all drugs on the market act by binding to these receptors.
- G-protein-coupled receptors are membrane-bound proteins
  - responsible for activating proteins called G-proteins.
- G-protein act as signal proteins
  - because they are capable of activating or deactivating membrane-bound enzymes.

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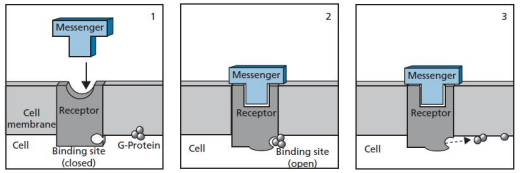

- The receptor protein is embedded within the membrane.
- The binding site for the chemical messenger exposed on the outer surface.
- On the inner surface, there is another binding site which is normally closed.
- When the chemical messenger binds to its binding site,
  - the receptor protein changes shape

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  - opening up the binding site on the inner surface.
- This new binding site is recognized by the G-protein which then binds.
- The G-protein is attached to the inner surface of the cell membrane.
  - It is made up of three protein subunits.
  - But once it binds to the receptor the complex is destabilized and fragments to a monomer and a dimer.

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Nucleic acids: structure and function

- There are two types of nucleic acid.
  - Deoxyribonucleic acid (DNA)
  - Ribonucleic acid (RNA)

Deoxyribonucleic acid (DNA)

- DHA has primary, secondary and tertiary structure.
- Primary structure
  - The primary structure of DNA is the way in which the DNA building blocks are linked together.

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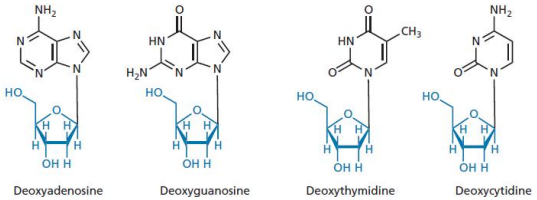

- **DHA has only four building blocks.**
  - ✓ the nucleoside deoxyadenosine
  - ✓ the nucleoside deoxyguanosine
  - ✓ the nucleoside deoxycytidine
  - ✓ the nucleoside deoxythymidine

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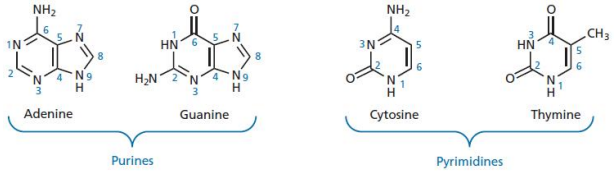
- **Each nucleoside is constructed from two components**
  - ✓ a deoxyribose sugar
  - ✓ a base
- **The sugar is the same and only the base is different.**
- **Two bicyclic purines (adenine and guanine).**
- **Two smaller pyrimidine structures (cytosine and thymine).**



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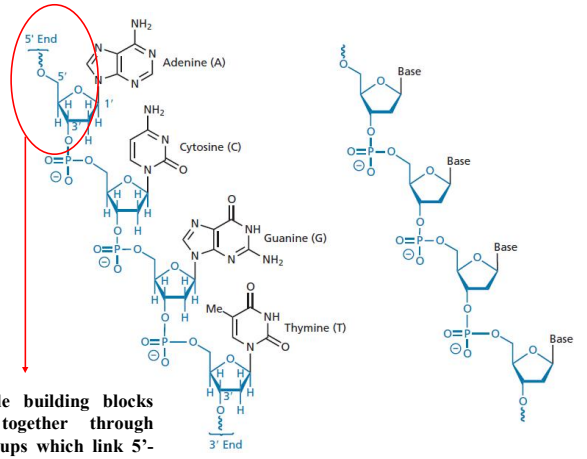

The nucleoside building blocks are joined together through phosphate groups which link 5'-hydroxyl group of one nucleoside unit to the 3'-hydroxyl group of the next

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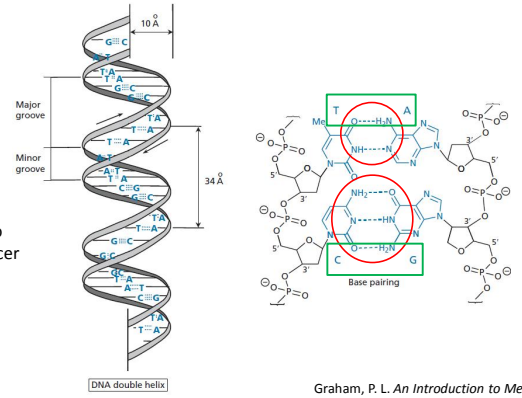
- **Secondary structure**
  - **The structure consists of two DNA chains arranged together in a double helix of constant diameter.**



Importance to some anticancer agents

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- Tertiary structure
  - The tertiary structure of DNA is often neglected or ignored.
  - But it is important to the action of the quinolone group of
    - ✓ antibacterial agents
    - ✓ anticancer agents
- DNA contains the genetic code for proteins.
- Responsible for the replication of the genetic code to the next generation.

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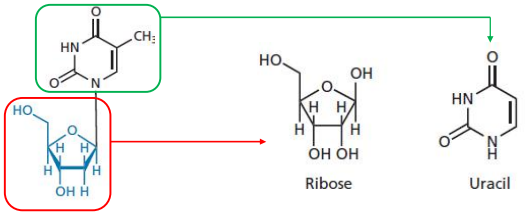
Ribonucleic acid (RNA)

- The primary structure of RNA is the same as that of DNA with two exceptions.
  - Ribose is the sugar component rather than deoxyribose.
  - Uracil replaces thymine as one of the bases.



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- Base-pairing
  - Adenine (A) pairing to uracil (U).
  - Cytosine (C) pairing to guanine (G).
- However, the pairing is between bases within the same chain.
  - It does not occur for the whole length of the molecule.
- RNA is not a double helix.
- Three main types of RNA molecules
  - messenger RNA (mRNA)
  - transfer RNA (tRNA)
  - ribosomal (rRNA)

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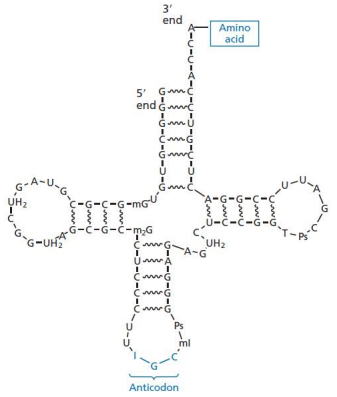
- Although DNA contains the genetic code for proteins,
  - it cannot produce these proteins directly.
- RNA takes on that role, acting as the "middle man" between proteins and DNA



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Drug targets

- Drug targets are macromolecules that have a binding site into which the drug fits and binds.
- Drugs act on molecular targets located in the cell membrane of cells or within the cells themselves.
- Most drugs bind to their targets by means of intermolecular bonds.
- The main molecular targets for drugs are
  - proteins (mainly enzymes, receptors, and transport proteins)
  - nucleic acids (DNA and RNA).

81

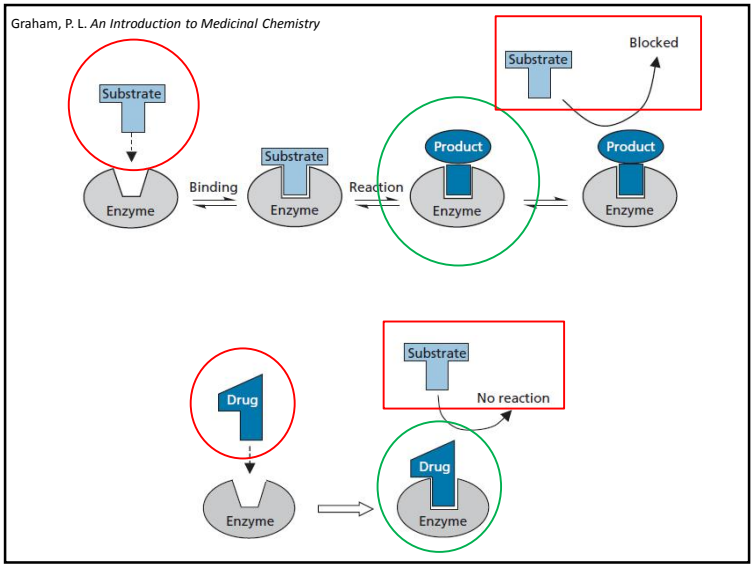
Enzymes as drug target

- Many important drugs act as enzyme inhibitors.
  - They prevent enzymes acting as catalysts for a particular reaction.

Inhibitors acting at the active site of an enzyme

- A molecule can be designed
  - which is similar to the natural substrate or product,
  - can fit the active site,
  - binds more strongly.

82



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- This is known as competitive inhibition.
  - The drug is competing with the natural substrate for the active site.
- The binding is reversible.
- However there are some irreversible inhibitors.
  - They can form a covalent bond to a key amino acid in the active site and block the enzyme permanently.
  - The amino acid being affected is either serine or cysteine.
  - Because these amino acids are often present in active sites and contain nucleophilic groups (-OH and –SH).

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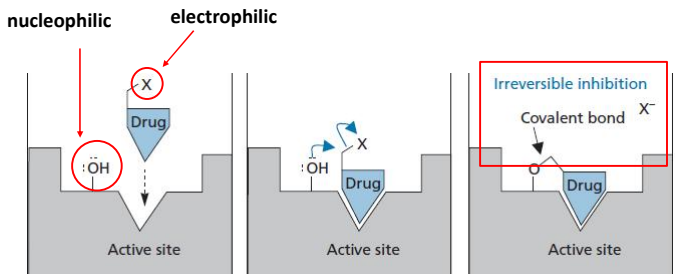

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Receptors as drug target

- Drugs that mimic the natural messengers and activate receptors are known as agonists.
  - They may have a similar structure to the natural ligand.
- Drugs that block receptors are known as antagonists.
  - They still bind to the receptor, but they do not activate it.
  - They prevent the natural messenger from binding.
- Antagonists tend to have more binding interactions than agonists and bind more strongly.

86

Design of agonists

- The following are the general requirements for the design of agonists.
  - The drug must have the correct binding groups.
  - The drug must have these binding groups correctly positioned.
  - The drug must be the right size for the binding site.

Design of antagonists

- The best way is to design a drug that is the right shape to bind to the receptor binding site.

87

Nucleic acids as drug target

- The interacting of drugs with DNA can be classified according to the following categories.
  - Intercalating agents
  - Topoisomerase poisons (non-intercalating)
  - Alkylating agents
  - Chain cutters
  - Chain terminators

88

Intercalating drugs

- Intercalating drugs are compounds that contain planar or heteroaromatic features.
  - ➢ They can slip between the base-pair layers of the DNA double helix.
- Once they are inserted between the nucleic acid base pairs
  - ➢ the aromatic/heteroaromatic rings are held there by van der Waals interactions with the base pairs above and below.

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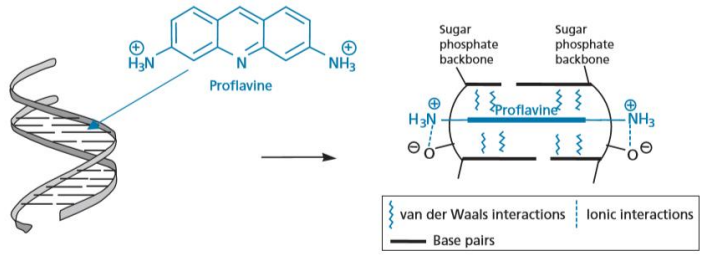

Topoisomerase poisons (non-intercalating)

- They block the action of topoisomerase (topoisomerase I and II)
  - ➢ Topoisomerases are enzymes that participate in the overwinding or underwinding of DNA.

90

Alkylating agents

- Alkylating agents are highly electrophilic compounds that react with nucleophiles to form strong covalent bonds.
- Drugs with two alkylating groups can react with a nucleic acid base on each chain of DNA to cross-link the strands
  - ➢ such that replication or transcription is disrupted.
- The drug could link two nucleophilic groups on the same chain.

91

Chain cutters

- "Chain cutters" cut the strands of DNA and prevent the enzyme DNA ligase from repairing the damage.
- They appear to act by creating radicals on the DNA structure.
  - ➢ These radicals react with oxygen to form peroxy species and the DNA chain fragments.

Chain terminators

- Chain terminators are drugs that act as "false substrates".

92

- They are incorporated into the growing DNA chain during replication.
- Once they have been added,
  - the chain can no longer be extended and chain growth is terminated.
- Chain terminators have to satisfy three conditions.
  - They have to be recognized by the DNA template.
  - They should have a triphosphate group.
  - Their structure must make it impossible for any further building blocks to be added.

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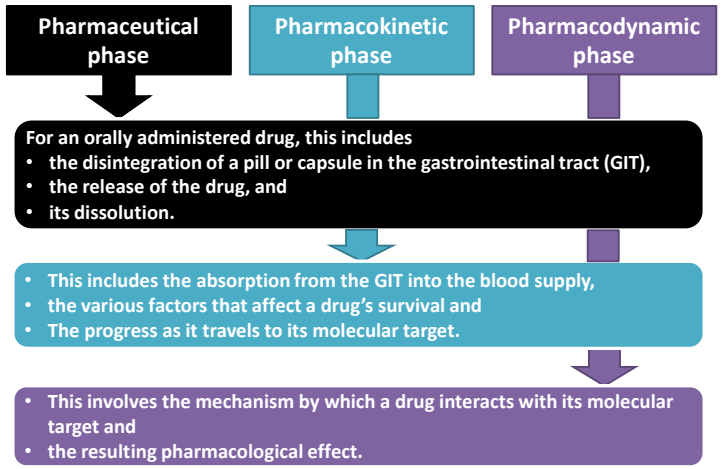
Drug action



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- The pharmacodynamic aspects of drug action
  - optimizing the binding interactions of a drug with its targets.
- Four main topics to consider in pharmacokinetics are
  - absorption
  - distribution
  - metabolism
  - excretion

95

Drug absorption

- In order to be absorbed efficiently from the GIT,
  - A drug must have the correct balance of water versus fat solubility.
- If the drug is too polar (hydrophilic),
  - it will fail to pass through the fatty cell membranes of the gut wall.
- If the drug is fatty (hydrophobic),
  - it will be poorly soluble in the gut and will dissolve in fat globules.

96

- Many drugs contain an amine functional group.
  - Amines are often involved in a drug's binding interactions with its target.
  - They are also the answer to the problem of balancing the dual requirements of water and fat solubility.
- Why and how ?
  - Amines are weak bases and many of the most effective drugs contain amine groups having a pK_a value in the range 6 – 8.
  - They are partially ionized at the slightly acidic and alkaline pHs present in the intestine and blood.

97

- They can easily equilibrate between their ionized and non-ionized forms.
- The presence of non-ionized form
  - ✓ allows them to cross cell membranes
- The presence of the ionized
  - ✓ gives the drug good water solubility
  - ✓ permits good binding interactions with its target binding site
- The extent of ionization at a particular pH can be determined by the Henderson–Hasselbalch equation.

98

$$\mathrm{pH} = \mathrm{p}K_\mathrm{a} + \log\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]}$$

- When the concentrations of the ionized and non-ionized amines are identical,
  - pH = pK_a
  - Drugs with a pK_a of 6 – 8 are approximately 50% ionized at blood pH (7.4).
- The hydrophilic/hydrophobic character of the drug is the major factor affecting absorption through the gut wall.

99

- Other factors that affect the absorption
  - Molecular weight (< 500)
  - Hydrogen bond donor groups (< 5)
  - Hydrogen bond acceptor groups (< 5)
  - Calculated log P value (< +5) (drug's hydrophobicity)
  - Food or other drugs in the gut
- Lipinski's rule of five
  - derived from an analysis of compounds from the World Drugs Index database.
  - Orally absorbed drugs

100

100

Drug distribution

- Once a drug has been absorbed,
  - it is rapidly distributed around the blood supply
  - distributed more slowly to the various tissues and organs.
- The rate and extent of distribution depends on various factors.
  - For example, the physical properties of the drug.
- Once a drug has been absorbed into the blood supply,
  - it is rapidly and evenly distributed throughout the blood supply within a minute.

101

- However, drugs do not stay confined to the blood supply.
- The drug has to leave the blood supply in order to reach organs and tissues.
  - There are pores between the cells.
  - They are large enough to allow most drug-sized molecules to pass though, but not large enough to allow the plasma proteins present in blood to escape.
  - Drugs do not have to cross cell membranes in order to leave the blood system.
  - They can be freely and rapidly distributed into the aqueous fluid surrounding the various tissues and organs of the body.

102

- Once a drug has reached the tissues, it can immediately be effective if its target site is a receptor situated in a cell membrane.
- There are many drugs that have to enter the individual cells of tissues in order to reach their target.
- Such drugs must be hydrophobic enough to pass through the cell membrane.
- The blood–brain barrier is an important barrier that drugs have to negotiate if they are to enter the brain.
  - Cells do not contain pores.
  - Drugs entering the brain have to dissolve through the cell membranes of the capillaries.

103

  - They also have to pass through the fatty cells coating the capillaries.
  - Polar drugs cannot enter the brain easily.

Drug metabolism

- When drugs enter the body, they are subject to attack from a range of metabolic enzymes.
- The role of this enzymes
  - is to degrade or modify the foreign structure
  - such that it can be more easily excreted.

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- Drugs undergo some form of metabolic reaction (in structures) known as metabolites.
  - They lose the activity of the original drug.
  - In some cases, they may retain a certain level of activity.
  - In exceptional cases, the metabolite may even be more active than the parent drug.
- Some metabolites can possess a different activity from the parent drugs, resulting in side effects or toxicity.

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Phase I and phase II metabolism

- The body treats drugs as foreign substances.
  - It has methods of getting rid of such chemical invaders.
- If the drug is polar,
  - it will be quickly excreted by the kidneys.
- If the drug is non-polar,
  - It is not easily excreted.
  - The purpose of drug metabolism is to convert such compounds into more polar molecules.

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- Phase I metabolism (reaction)
  - Polar functional groups are added to the drugs by non-specific enzymes (cytochrome P450 in liver).
  - The overall drug is more polar and water soluble.
  - It is more likely to be excreted when it passes through the kidneys.
  - An alternative set of enzymatic reactions can reveal masked polar functional groups already present.
    - ✓ For example, demethylate a methyl ether to reveal a more polar hydroxyl group.

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  - They generally involve oxidation, reduction, and hydrolysis.
  - Most of these reactions occur in the liver,
    - ✓ but some can also occur in the gut wall, blood plasma, and other tissues.
    - ✓ For example, the hydrolysis of esters and amides.
- Phase II metabolism (reaction)
  - Reactions also occur mainly in the liver.
  - Most of these reactions are conjugation reactions.

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- ✓ A polar molecule is attached to a suitable polar "handle" that is already present on the drug,
- ✓ or has been introduced by a phase I reaction.

Phase I transformations catalyzed by cytochrome P450 enzymes

- **Haemoproteins (containing haem and iron)**
  - ➢ **They are enzymes that constitute the cytochrome P450 family.**
  - ➢ **They are the most important metabolic enzymes.**
  - ➢ **They are located in liver cells.**

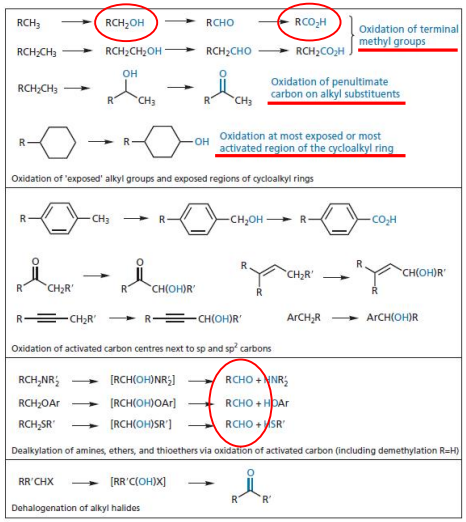
109

- **They catalyze a reaction that splits molecular oxygen.**
  - ➢ **Such that one of the oxygen atoms is introduced into the drug and the other ends up in water.**
- **They belong to a general class of enzymes called the monooxygenases.**

$$\text{Drug—H} + O_2 + \text{NADPH} + H^+ \xrightarrow{\text{Cytochrome P450 enzymes}} \text{Drug—OH} + \text{NADP} + H_2O$$

- **There are at least 33 different cytochrome P450 (CYP) enzymes, grouped into four main families.**
- **The reactions catalyzed by cytochrome P450 enzymes are shown.**

110



Oxidative reactions catalyzed by cytochrome P450 enzymes on saturated carbon centres

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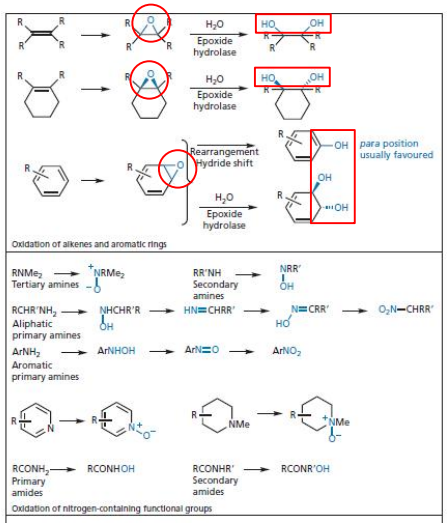

Oxidative reactions catalyzed by cytochrome P450 enzymes on heteroatoms and unsaturated carbon centres

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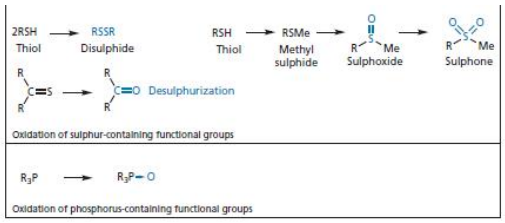

Phase I transformations catalyzed by flavin-containing monooxygenases

- **Flavin-containing monooxygenases**
  - **Another group of metabolic enzymes present in the endoplasmic reticulum of liver cells.**

113

- **They are responsible for metabolic reactions involving oxidation at**
  - **nucleophilic nitrogen, sulphur, and phosphorus atoms.**
  - **But not in carbon atoms.**

Phase I transformations catalyzed by other enzymes

- **There are several oxidative enzymes in various tissues around the body that are involved in the metabolism.**
- **They also play a role in drug metabolism.**

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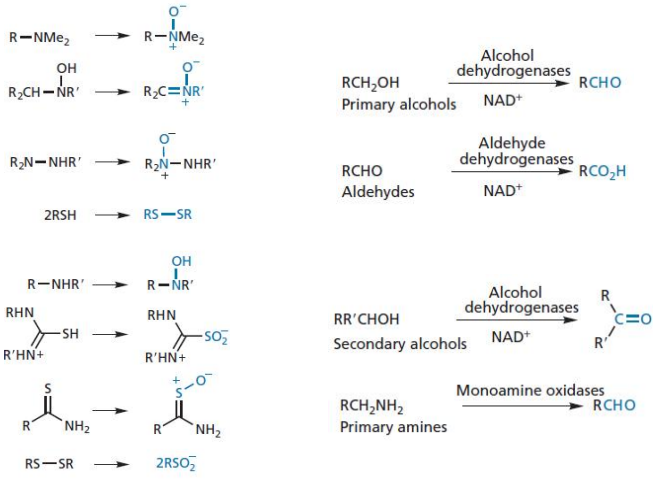

Phase I reactions catalyzed by flavin monooxygenases

Phase I oxidative reactions catalyzed by miscellaneous enzymes

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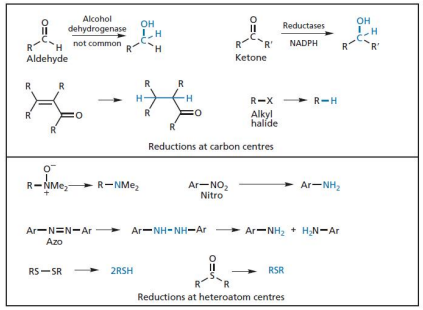
- **Reductive phase I reactions are less common than oxidative reactions.**
  - **Reductions of aldehyde, ketone, azo and nitro functional groups have been observed in specific drugs.**



Phase I reductive reactions

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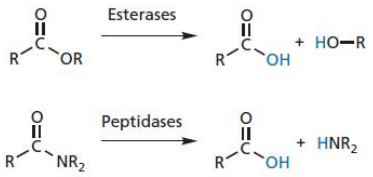
- **The hydrolysis of esters and amides is a common metabolic reaction.**
  - **They are catalyzed by esterases and peptidases, respectively.**



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Phase II transformations

- **Most phase II reactions are conjugation reactions catalyzed by transferase enzymes.**
- **Glucuronic acid conjugation is the most common.**
  - **Phenols, alcohols, hydroxylamines, and carboxylic acids form *O*-glucuronides by reaction with UDFP-glucuronate.**
  - **A highly polar glucuronic acid molecule is attached to the drug.**
  - **The resulting conjugate is excreted in the urine.**

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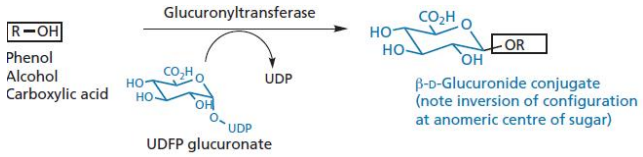
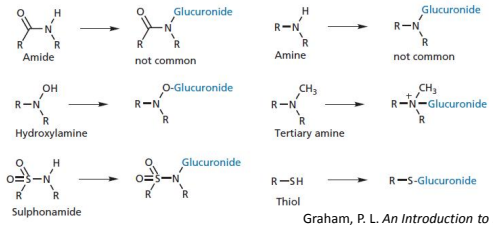


- **A number of other functional groups, such as sulphonamides, amides, amines, and thiols can react.**



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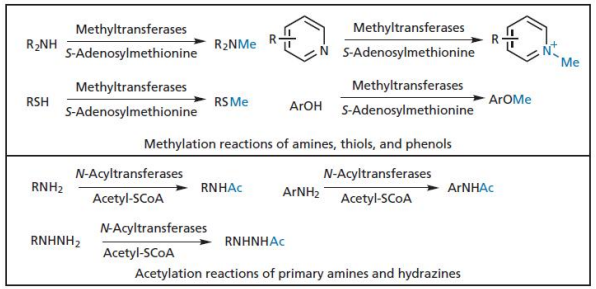
- **Not all phase II reactions result in increased polarity.**
- **Methylation and acetylation are important phase II reactions which usually decrease the polarity of the drug.**



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- Certain drugs are also capable of inhibiting or promoting cytochrome P450 enzymes.
  - Drug-drug interaction
  - The presence of one drug affects the activity of another.

Drug excretion

- Drugs and their metabolites can be excreted from the body by a number of routes.
- Volatile or gaseous drugs are excreted through the lungs.
- Drugs can also be excreted through saliva and breast milk.

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- The kidneys are the principal route by which drugs and their metabolites are excreted.
  - Kidneys filter the blood of waste chemicals (drugs) and these chemicals are removed in the urine.

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